DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

A method comprising reacting a nucleoside phosphoramidite with a support bound 1 (original).

oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one

unprotected internucleoside linkage selected from the group consisting of phosphate linkages,

phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

aromatic heterocyclic amine, or a guanidine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or

unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate

anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate

anion.

2 (original). The method of claim 1 wherein said neutralizing agent is a salt of formula D⁺E.

Page 2 of 24

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

The method of claim 2 wherein E is a tetrazolide anion. 3 (original).

The method of claim 1 wherein E is 1H-tetrazolide anion, 5-methylthio-1H-4 (original).

tetrazolide anion, 5-ethylthio-1H-tetrazolide anion or 1-phenyl-5-thiol-1H-tetrazolide anion.

The method of claim 1 wherein E is 1H-tetrazolide anion. 5 (original).

The method of claim 3 wherein D⁺ is a protonated form of any of an alkyl, alkenyl 6 (original).

or alkynyl amine having from one to about 20 carbons, an aliphatic heterocyclic amine, an aromatic

heterocyclic amine, or a guanidine.

7-10 (canceled).

A method comprising reacting a nucleoside phosphoramidite with 11 (previously presented).

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of an aromatic heterocyclic amine; and

Page 3 of 24

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

E is a tetrazolide anion.

A method comprising reacting a nucleoside phosphoramidite with 12 (previously presented).

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D+E wherein:

D⁺ is a protonated form of a mono-, di- or trialkyl pyridine that is

optionally substituted with an amino group; and

E is a tetrazolide anion.

13 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine,

2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-

butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine; and

Page 4 of 24

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

E is a tetrazolide anion.

14 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D+E wherein:

D⁺ is a protonated form of an alkylamino substituted pyridine; and

E- is a tetrazolide anion.

15 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of 4-dimethylaminopyridine; and

E is a tetrazolide anion.

16-20 (canceled).

Page 5 of 24

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

21 (original). The method of claim 3 wherein E is 1H-tetrazolide anion.

22-35 (canceled).

36 (previously presented). A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D+E- wherein:

D⁺ is a protonated form of an aromatic heterocyclic amine; and

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

37 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group; and

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

38 (previously presented). A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

Office Action Dated: December 2, 2003

aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

39 (previously presented). A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of an alkylamino substituted pyridine; and

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate

anion.

40 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a protonated form of 4-dimethylaminopyridine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or

unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate

anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate

anion.

41-46 (canceled).

47 (original). The method of claim 3 wherein D⁺ is a protonated form of trimethyl amine,

Page 9 of 24

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, tbutyldimethyl amine, diisopropylethyl amine, N,N,N',N'-tetramethyl-1,2-diaminoethane, DBU, -methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, -ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene, 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6tri(t-butyl)pyridine, 4-dimethylaminopyridine, or N,N,N'N'-tetramethylguanidine, or

trimethyloctylammonium, or triethylbenzylammonium cation; and E is 1H-tetrazolide anion, 4,5-dicyanoimidazolide anion, methylsulfonate anion,

trifluoromethylsulfonate anion, methylphenylsulfonate anion, trifluoromethylphenylsulfonate anion,

tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium,

tetrafluoroborate anion, hexafluorophosphate anion, or trifluoroacetate anion.

48 (currently amended). A method of forming an internucleoside linkage comprising reacting a phosphoramidite of formula:

Page 10 of 24

Office Action Dated: December 2, 2003

wherein:

L₁ is an internucleoside linkage;

 n_1 is 0 to about 100;

R₁ is a hydroxyl protecting group;

R₂ is a 2'-substituent group, said 2'-substituent group being fluoro, chloro, bromo, O-alkyl, O-alkylamino, O-alkylamino, O-alkylamino, O-alkylaminoalkyl, oralkylaminoalkyl, oralkylaminoalkylaminoalkyl, oralkylaminoalkylaminoalkyl, oralkylaminoalkylaminoalkylaminoalkylaminoalk

DOCKET NO.: ISIS-4682 Application No.: 09/775,967

Office Action Dated: December 2, 2003

wherein:

E is C_1 - C_{10} alkyl, $N(R_{12})(R_{13})$ or $N=C(R_{12})(R_{13})$;

each R₁₂ and R₁₃ is, independently, H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₁₂ and R₁₃, together, are a nitrogen protecting group or are joined in a ring structure that includes at least one additional heteroatom selected from N and O;

 R_{14} is OX_1 , SX_1 , or $N(X_1)_2$;

each X_1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)Z_1$, $C(=O)N(H)Z_1$ or $OC(=O)N(H)Z_1$:

 Z_1 is H or C_1 - C_8 alkyl;

 L_1 , L_2 and L_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms, said heteroatoms being selected from oxygen, nitrogen and sulfur, wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

 \underline{Y}_m is \underline{C}_1 - \underline{C}_{10} alkyl or haloalkyl, \underline{C}_2 - \underline{C}_{10} alkenyl, \underline{C}_2 - \underline{C}_{10} alkynyl, \underline{C}_6 - \underline{C}_{14} aryl, $\underline{N}(\underline{R}_{12})(\underline{R}_{13})$ \underline{OR}_{12} , halo, \underline{SR}_{12} or \underline{CN} ;

each q₁ is, independently, an integer from 2 to 10;

Office Action Dated: December 2, 2003

each q_2 is 0 or 1;

p is an integer from 1 to 10; and

q₃ is an integer from 1 to 10;

provided that when p is 0, q₃ is greater than 1;

B is a nucleobase;

Q is O or S;

Pg is a phosphoryl protecting group;

with a compound of formula:

HO
$$R_2$$
 R_3
 R_3
 R_2

wherein

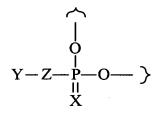
R₃ is a linker connected to a solid support;

n is from 1 to 100; and

L is an internucleoside linkage of formula:

DOCKET NO.: ISIS-4682 Application No.: 09/775,967

Office Action Dated: December 2, 2003



wherein:

Z is O or S;

X is O or S; and

Y is a phosphoryl protecting group or a negative charge;

provided that at least one Y is a negative charge;

wherein said reaction is performed in the presence of a neutralizing agent;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

49 (original). The method of claim 48 wherein said neutralizing agent is a salt of formula D^+ E^- .

DOCKET NO.: ISIS-4682

Application No.: 09/775,967

Office Action Dated: December 2, 2003

50 (original). The method of claim 49 wherein E is a tetrazolide anion.

51 (original). The method of claim 48 wherein E⁻ is 1H-tetrazolide anion, 5-methylthio-1H-tetrazolide anion, 5-ethylthio-1H-tetrazolide anion or 1-phenyl-5-thiol-1H-tetrazolide anion.

52 (original). The method of claim 48 wherein E is 1H-tetrazolide anion.

53-55 (canceled).

56 (original). The method of claim 50 wherein D⁺ is a protonated form of an aromatic heterocyclic amine.

57 (original). The method of claim 50 wherein D⁺ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

58 (original). The method of claim 50 wherein D⁺ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

59 (original). The method of claim 50 wherein D^+ is a protonated form of an alkylamino substituted pyridine.

60 (original). The method of claim 50 wherein D⁺ is a protonated form of 4-dimethylaminopyridine.

61-65 (canceled).

Page 15 of 24

Office Action Dated: December 2, 2003

66 (original). The method of claim 50 wherein E is 1H-tetrazolide anion.

67-80 (canceled).

81 (original). The method of claim 48 wherein D⁺ is a protonated form of an aromatic heterocyclic amine.

82 (original). The method of claim 48 wherein D⁺ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

83 (original). The method of claim 48 wherein D⁺ is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

84 (original). The method of claim 48 wherein D⁺ is a protonated form of an alkylamino substituted pyridine.

85 (original). The method of claim 48 wherein D^+ is a protonated form of 4-dimethylaminopyridine.

86-91 (canceled).

92 (original). The method of claim 50 wherein D⁺ is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, t-butyldimethyl amine, diisopropylethyl amine, N,N,N',N'-tetramethyl-1,2-diaminoethane, DBU, N-

Office Action Dated: December 2, 2003

methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, N-ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene, 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine, 4-dimethylaminopyridine, or N,N,N'N'-tetramethylguanidine, or tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation; and

E is 1H-tetrazolide anion, 4,5-dicyanoimidazolide anion, methylsulfonate anion, trifluoromethylsulfonate anion, methylphenylsulfonate anion, trifluoromethylphenylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or trifluoroacetate anion.

93 (original). The method of claim 50 wherein Q is O; Z is O;

Pg is β -cyanoethyl, methyl, (N-methyl-N-benzoylamino)ethyl, (N-ethyl-N-benzoylamino)ethyl, 2-[N-methyl-N-(4-methoxybenzoyl)amino]ethyl, 2-(N-isopropyl-N-benzoylamino)ethyl, 2-[N-ethyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-methyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-ethyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-(thionobenzoylamino)ethyl, 3-(thionobenzoyl-amino)propyl, 2-(N-phenylthiocarbamoylamino)ethyl, 2-[(1-naphthyl)carbamoyloxy]ethyl, diphenyl-silylethyl, δ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl; and

Y is β -cyanoethyl, allyl, methyl, (N-methyl-N-benzoylamino)ethyl, (N-ethyl-N-benzoylamino)ethyl, 2-[N-methyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-isopropyl-N-benzoylamino)ethyl, 2-[N-ethyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-methyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-ethyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-(thionobenzoylamino)ethyl, 2-(N-phenylthiocarbamoylamino)ethyl, 2-[(1-naphthyl)carbamoyloxy]ethyl, diphenylsilylethyl, δ -cyanobutenyl, cyano p-xylyl, methyl-N-

Office Action Dated: December 2, 2003

trifluoroacetyl ethyl, acetoxy phenoxy ethyl, or a negative charge.

94 (original). The method of claim 48 wherein:

said neutralizing agent is a salt of formula D+E;

E is a tetrazolide anion:

D⁺ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group;

Q is O;

Z is O;

 R_4 and R_5 are each diisopropyl, or R_4 and R_5 together with the nitrogen atom to which they are attached form morpholine;

Pg is β -cyanoethyl, methyl, diphenylsilylethyl, δ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl; and

Y is β -cyanoethyl, allyl, methyl, diphenylsilylethyl, δ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl or a negative charge.

95 (original). The method of claim 94 wherein:

E is 1H-tetrazolide anion;

D⁺ is a protonated form of dimethylaminopyridine;

Pg is β -cyanoethyl, diphenylsilylethyl, δ -cyanobutenyl, cyanop-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl; and

Y is β -cyanoethyl, allyl, diphenylsilylethyl, δ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl, acetoxy phenoxy ethyl or a negative charge.

96 (original). A method comprising the steps of:

(a) providing a solid support having a 5'-O-protected phosphorus-linked oligomer bound

Office Action Dated: December 2, 2003

thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group;

- (b) deprotecting the 5'-hydroxyl of the 5'-O-protected phosphorus-linked oligomer with a deprotecting reagent;
- (c) washing the deprotected phosphorus-linked oligomer on the solid support with a solution containing a neutralizing agent;
- (d) reacting the deprotected 5'-hydroxyl with an 5'-protected nucleoside phosphoramidite to produce a phosphite triester linkage therebetween; and
- (e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage; and

optionally repeating steps b through e at least once for subsequent couplings of additional nucleoside phosphoramidites;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

97 (original). A method comprising the steps of:

(a) providing a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that

Office Action Dated: December 2, 2003

does not bear a phosphoryl protecting group;

(b) deprotecting the 5'-hydroxyl of the 5'-O-protected phosphorus-linked oligomer with a deprotecting reagent to form a support bound 5'-deprotected phosphorus-linked oligomer;

- (c) optionally washing the deprotected phosphorus-linked oligomer on the solid support;
- (d) contacting the support bound 5'-deprotected phosphorus-linked oligomer with a solution comprising a 5'-protected nucleoside phosphoramidite to produce a phosphite triester linkage therebetween, wherein said solution further comprises a neutralizing agent; and
- (e) oxidizing or sulfurizing the phosphite triester linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage; and

optionally repeating steps b through e at least once for subsequent couplings of additional nucleoside phosphoramidites;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D⁺E⁻ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

98 (previously presented). A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula D⁺E⁻ wherein:

a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

Office Action Dated: December 2, 2003

E⁻ is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

99 (previously presented). A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula D⁺E⁻ wherein:

E is a tetrazolide anion; and

D⁺ is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

100 (previously presented). A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula D⁺E⁻ wherein:

E is 1H-tetrazolide anion; and

D⁺ is a protonated form of dimethylaminopyridine.

101 (previously presented). A composition comprising:

- -- a 5'-protected nucleoside phosphoramidite;
- -- a salt of formula D⁺E⁻ wherein:

D⁺ is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion; and

-- a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said

phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does

Office Action Dated: December 2, 2003

not bear a phosphoryl protecting group.

102 (canceled)

103 (original). The composition of claim 100 further comprising a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group.

104. (previously presented) The method of claim 50 wherein D+ is a protonated form of alkyl, alkenyl or alkynyl amine having from one to about 20 carbons, an aliphatic heterocyclic amine, an aromatic heterocyclic amine, or a guanidine.

105. (Canceled)